The Pathogenesis of Peptic Ulcer

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• Peptic ulcers of the stomach and duodenum look much alike and the reaction around them is nonspecific, yet other evidence indicates that ulcers in the two locations do not represent the same disease. It is suggested that a common causal factor is the digestive effect of gastric juice, and that hypersecretion may produce duodenal ulcer without any predisposing change in the relatively susceptible duodenum. The development of a gastric ulcer, which may occur without hypersecretion, presumably requires some previous alteration of the normally resistant gastric mucosa. Focal metaplasia of the gastric mucosa to tissue resembling the lining of the small intestine, which is observed frequently in association with gastric ulcer, may be a factor in providing decreased resistance to peptic injury.

THE TERM "PEPTIC ULCER," in use since 1882, and applied to ulcers that occur in various regions of the alimentary tract reached by gastric juice, implies a common cause related to peptic activity. Most discussions make no clear etiologic distinctions between gastric and duodenal ulcers. The most recent edition of one of the commonly used textbooks of pathology[1] contains the statement that these two lesions "in all likelihood have a similar etiology."

The tissue reaction around peptic ulcers is nonspecific. There is fibrosis at the base related to the duration of the lesions, but no clues concerning pathogenesis are provided by the structure. This presentation will consider evidence of other sorts relating to ulcer pathogenesis, particularly with respect to the role of digestion by gastric juice and to the question of whether gastric and duodenal ulcer represent the same disease.

There is much evidence to support the dictum expressed by Schwartz[10] in 1910, which can be translated as "no acid, no ulcer." The absence of peptic ulcer in patients with pernicious anemia is striking. No report could be found of either gastric or duodenal ulcer in association with this disease where gastric achylia was present, and the author has never observed either type of ulcer when there were no parietal cells. The well-known occurrence of jejunal ulcer after gastroenterostomy in man or following the Mann-Williamson procedure in dogs, and the development of entirely comparable ulcers adjacent to Meckel's diverticula containing gastric mucosa provide strong evidence for a role of gastric juice in the production of these intestinal ulcers. Wells and MacPhee[12] recently emphasized the inverse relationship of the incidence of postoperative jejunal ulcer to the amount of gastric mucosa removed by the surgeon.

Of note also is the relatively recent observation that the administration of cortisone or corticotropin (ACTH) may induce peptic ulcer at the same time as gastric secretion is augmented.[6]

To these experiences may be added the frequent and predictable appearance of ulcers in animals treated with continuously acting histamine[11] and the regular occurrence of duodenal ulcers in dogs given continuous administration of 0.2 per cent pepsin in 0.15 normal hydrochloric acid by gastrostomy for several days.[5] This concentration of acid approximates the maximum which can be secreted by the gastric mucosa.

In relation to the possible role of acid and pepsin in the production of ulcers it is important to keep in mind not only the capacity of the mucosa to produce digestive secretions, but also the mechanisms which may inhibit their effect. Chief among these is the buffering influence of food, which may be sufficient to neutralize the free acid in the stomach completely. Hay, Varco, Code and Wangensteen[7] showed that proper feeding of animals may prevent the development of ulcer after histamine treatment, and like phenomena were observed by the author in similar experiments. Differences in eating habits, then, particularly in individuals with gastric hypersecretion, should be expected to produce considerable differences in exposure of the mucosa to active gastric juice. It seems probable that the development of peptic ulcers following severe burns, cerebral operations and head injuries may be prominently influenced by lack of protective food in the stomach of the acutely ill patients.

Alkaline duodenal content may be regurgitated into the stomach, and although this mechanism is unpredictable, it is a potential reducing influence upon the digestive activity of the stomach content.

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The foregoing observations suggest an essential role of active gastric juice in the pathogenesis of gastric and duodenal ulcer in man, but there are several reasons for doubting that this is the only factor, or that it is even the major cause in some cases. Among these are some facts which suggest that gastric and duodenal ulcer may be distinctly different processes.

First is the different secretory pattern in patients with the different lesions. Many reports indicate hypersecretion in stomachs of patients with duodenal ulcer but not in those with gastric ulcer. This difference is particularly easy to recognize when the "basal" secretory activity is measured, as Bloomfield and French[2] demonstrated in 1938. This basal secretion is that which occurs without specific stimulation and so is particularly important because it represents the gastric secretion at a time when no buffering food is present in the stomach.

This difference of gastric function in patients with gastric and duodenal ulcer is paralleled by differences in stomach size. It was reported recently[3] that stomachs from patients with duodenal ulcer are nearly always larger than average and have a larger amount of acid and pepsin-secreting mucosa, while those from patients with gastric ulcer do not have these peculiarities.

Another anatomical difference in the two types of cases relates to the nature of the so-called chronic gastritis which is present. In nearly all cases of both types of ulcer there is infiltration of the gastric mucosa in the pyloric zone, or antrum, by plasma cells and lymphocytes, and this relation of ulcer to chronic gastritis has been noted repeatedly in the literature. Little attempt has been made, however, to differentiate between mucosal changes in gastric and duodenal ulcer cases. It has been suggested[4] that focal gastric mucosal metaplasia to glands of intestinal type may have a significance different from that of other changes which are included under the name of gastritis. This replacement mucosa is characterized by the presence of Paneth cells, inhabitants of normal intestinal mucosa, which are not seen in the normal stomach. In a comparative study it was noted that the incidence of metaplasia of this type in the gastric antrum was twice as frequent in cases of gastric ulcer as in controls or in association with duodenal ulcer (Table 1). The specimens bearing these ulcers were obtained at autopsy soon after death and were examined carefully in comparison with control cases of similar age and sex, factors which relate to the occurrence of gastric mucosal metaplasia.

Most of the metaplasia was situated at a distance from the ulcer; it was not simply a repair phenomenon at the ulcer margins. The possibility that it represents healed superficial ulcers in stomachs

TABLE 1.—*Frequency of focal gastric antral mucosal metaplasia in patients with chronic gastric and duodenal ulcer.*

	No. of Cases	No. with Metaplasia	Pct. with Metaplasia
Chronic gastric ulcer or scar	33	26	79
Matched controls	66	27	41
Chronic duodenal ulcer or scar	39	14	36
Matched controls	78	32	41

TABLE 2.—*Incidence of peptic ulcer in 3,400 autopsies.*

Location	Cases	Incidence (Per Cent)	Multiple Ulcers (Pct. of Ulcer Cases)	Combination of Locations (Pct. of Ulcer Cases)
Duodenum	122	3.6	34	11
Stomach	105	3.1	35	12

prone to development of ulcers has been suggested and cannot be certainly ruled out. In recognized healed ulcers, however, and at the borders of healing ulcers, the repaired mucosa has a different appearance, and does not assume the specific character of intestinal mucosa with recognizable Paneth cells.

Ulcers of the stomach and duodenum might be expected to occur together as frequently as multiple ulcers appear in the same region if they are the product of the same causal factors. In a study of 3,400 autopsies on adult individuals performed over a ten-year period, multiple ulcers or ulcer scars in the same region (either stomach or duodenum) were found in about 35 per cent of the ulcer cases, while associated lesions in the two different regions occurred only one-third as frequently (Table 2). This incidence of associated gastric and duodenal ulcers is less than that which should exist if the same causes were involved in both.

These observations suggest fundamental differences in pathogenesis of gastric and duodenal ulcer and consequently indicate a need to consider the presence of factors other than digestive activity alone in the production of peptic ulcers. Such additional factors presumably modify mucosal resistance to peptic injury.

The normal stomach is quite resistant to acid and pepsin, as an essential feature of its digestive role. Deficiency in this resistance as a cause of ulcer is an old idea, and measured modifications in susceptibility to acid-pepsin injury have been produced in animals by various means. Among the mechanisms suspected as contributing to local reduction of mucosal resistance in man are vascular narrowing, ischemia due to shock, intoxications, irritation of foods, alterations in the surface protective layer of mucus, and vitamin deficiency. Clear proof of the influence of these or other possible mechanisms in the production of human peptic ulcer would be very difficult to identify since the operation of such factors might be transient or inconspicuous.

Recognizing that direct evaluation of factors such as these would be almost impossible in man, the author approached the question of whether some evidence of reduced resistance might be recognizable in the gastric mucosal structure. The change which presents itself as possibly providing this evidence is the focal mucosal metaplasia described above, which appears with unusual frequency in association with gastric ulcer and affects principally the pyloric zone, or antrum—the region in which practically all gastric ulcers are found.

It is possible that this altered mucosa of the intestinal type is itself less resistant to the action of gastric juice, in view of demonstrations that intestinal mucosa in animals is more susceptible than gastric mucosa to injury by the elements of gastric juice.[8, 9] A greater susceptibility of intestinal mucosa to peptic injury would provide an explanation for the predominance of ulcers in the duodenum when no gastric mucosal metaplasia is present, and it is tempting to suspect that gastric mucosal metaplasia might represent a reason for the development of comparable ulcers in the stomach even in the presence of relatively low gastric secretory activity. Inasmuch as metaplastic change could be regarded only as a predisposing cause, the lack of better correlation with the occurrence of gastric ulcer can be explained, and the author believes that the possibility of a predisposing role of mucosal metaplasia of the intestinal type should not be neglected. It is possible that a metaplastic alteration which is not distinctly recognizable as intestinal mucosa might also represent decreased resistance of the gastric mucosa.

CONCLUSION

The observations herein outlined represent an incomplete survey of the large number of studies which bear upon the ulcer problem, but they point to certain suggestions concerning the pathogenesis of peptic ulcer which can be expressed in the following hypothesis: The destructive mechanism which produces peptic ulcer is peptic digestion in an acid medium. This may require little predisposing change in the relatively susceptible jejunal mucosa after gastroenterostomy, in the mucosa of the ileum adjacent to a secreting Meckel's diverticulum, or in the duodenum when gastric secretory activity is high and there is inadequate neutralization of the gastric juice. The normal stomach, by contrast, is resistant to gastric juice even when it is concentrated. If acid and pepsin concentrations are low, the duodenal mucosa also resists injury; but even with a reduced secretory capacity of the stomach, abnormalities in its antral portion, perhaps represented by the intestinal type of mucosal metaplasia, may provide sufficient reduction in resistance of this region to permit development of gastric ulcer.

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REFERENCES

1. Anderson, W. A. D.: Textbook of Pathology, St. Louis, 1953.

2. Bloomfield, A. L., and French, L. R.: Basal gastric secretion in cases of peptic ulcer: Relation of acidity to healing of ulcer, J. C. I., 17:667-670, 1938.

3. Cox, A. J.: Stomach size and its relation to chronic peptic ulcer, Arch. Path., 54:407-422, 1954.

4. Cox, A. J.: Chronic atrophic gastritis; identification of different varieties, J. Nat. Cancer Inst., 10:523-526, 1949.

5. Fogelman, M. J., Grossman, M. I., and Ivy, A. C.: Further studies on the effect of continuous intragastric infusion of acid and pepsin in dogs, Surgery, 25:60-67, 1949.

6. Gray, S. J., Benson, J. A., Jr., Reifenstein, R. W., and Spiro, H. M.: Chronic stress and peptic ulcer, J.A.M.A., 147:1529-1537, 1951.

7. Hay, L. J., Varco, R. L., Code, C. F., and Wangensteen, O. H.: The experimental production of gastric and duodenal ulcers in laboratory animals by the intramuscular injection of histamine in beeswax, Surg., Gyn. and O., 75: 170-182, 1942.

8. Mann, F. C., and Bollman, J. L.: Experimentally produced peptic ulcers, J.A.M.A., 99:1576-1582, 1932.

9. Mathes, M.: Untersuchugen über die Pathogenese des Ulcus rotundum ventriculi und über den Einfluss von Verdauungsenzym auf lebendes und todes Gewebe, Beitr. z. path. Anat. U. Z. allg. Path., 13:309-364, 1893.

10. Schwartz, K.: Ueber penetrierende Magen- und Jejunalgeschwüre, Beitr. kl. Chir., 67:96-128, 1910.

11. Walpole, S. H., Varco, R. L., Code, C. F., Wangensteen, O. H.: Production of gastric and duodenal ulcers in the cat by intramuscular implantation of histamine, Proc. Soc. Exp. Biol. and Med., 44:619-621, 1940.

12. Wells, C., and MacPhee, I. W.: Partial gastrectomy: ten years later, Brit. M. J., 2:1128-1132, 1954.